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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 14 1992

MEMORANDUM

SUBJECT: Fifth Carcinogenicity Peer Review of Propiconazole

FROM: Elizabeth Doyle, Ph.D., Section Head E.A. Doyle 8/6/92
Review Section IV, Tox Branch II (H7509C)

and
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Science Analysis and Coordination Branch
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TO: Susan Lewis
Product Manager #21
Herbicide/Fungicide Branch
Registration Division (H7505C)

The Health Effects Division Carcinogenicity Peer Review Committee met on April 15, 1992 to discuss and evaluate the weight-of-the-evidence on propiconazole with particular reference to its carcinogenic potential.

The Peer Review Committee agreed that propiconazole should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Karl Baetcke

for Marcia Van Gemert James N. Rowe 8/10/92

Reto Engler

Robert Beliles

Lucas Brennecke

Marion Copley

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George Ghali

Jean Parker

Hugh Pettigrew

William Sette

Yin-Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Elizabeth Doyle[1] E. A. Doyle 8/6/92

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp Penelope A. Fenner-Crisp

William L. Burnam

Kerry Dearfield

Esther Rinde

Julie Du

Richard Hill

for John Quest James N. Rowe 8/10/92

4. Other Attendees: (Observers)

Eve Andersen (Clement)
Jon Fleuchaus
Ann Clevenger
Jim Rowe
Robert Friche
Lori Brunsman
Linnea Hansen

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

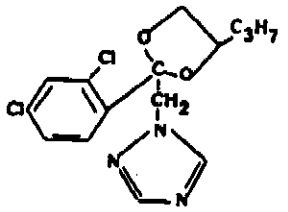
B. Material Reviewed:

The material available for review consisted of DER's, and other data summaries prepared by Elizabeth Doyle; tables and statistical analysis by Bernice Fisher. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by Ciba-Geigy Corp.

C. Background Information:

The Caswell (or Tox Chem) Number of propiconazole is 323EE
The Chemical Abstracts Registry Number (CAS No.) is 60207-90-1.

The structure of propiconazole is



Propiconazole has to date been the subject of four Peer Reviews and one SAP meeting. The following summaries of the preceding meetings are taken, in part, from the fourth Peer Review Document for this compound.

1. Initial Peer Review Committee Meeting Findings

The chemical was originally evaluated by the Peer Review Committee on January 15, 1987 and was classified as a Group C (possible human) carcinogen with a recommendation made for the quantification of estimated potential human risk using a linearized low-dose extrapolation. The classification was based upon the increased incidence of hepatocellular adenomas, carcinomas, and adenomas/carcinomas combined in CD1 male mice at 2500 ppm, the highest dose tested. The increase was statistically significant by pairwise comparison and trend analysis. The Committee found that the tumors progressed at an accelerated rate in the treated animals. There were no indications of treatment-related hepatocytic hyperplasia or necrosis. The incidence of nonneoplastic lesions in treated mice of both sexes, and neoplastic lesions in females were comparable to controls. The Committee felt, at this time, that the high dose might have been excessively toxic in males, based upon increased mortality in the first 52 weeks of the study, and the elevation of liver enzymes (SAP, SGOT, SGPT). There was also an increase in liver weight in the mid-, and high-dose males at interim and terminal sacrifice. Statistically significant increases in liver weights at interim and terminal sacrifice suggested that for females the high-dose level was appropriate for testing the carcinogenic potential of propiconazole.

In a second carcinogenicity study in Sprague-Dawley CD rats, treatment did not alter the spontaneous tumor profile for this strain under the conditions tested.

The group C classification was supported further by the structural similarity of propiconazole to other triazole fungicides such as Bayleton, Baytan, and etaconazole, all of which were reported to be associated with increased incidence of hepatocellular adenomas in male or female mice or both.

2. FIFRA Scientific Advisory Panel Evaluation

The Peer Review Committee's decision was presented to the FIFRA Scientific Advisory Panel (SAP) on March 2, 1988. The Panel did not concur with the Committee's overall assessment of the weight-of-evidence on the carcinogenicity of propiconazole. The Panel recommended placing the chemical in Group D. The Panel indicated that "there is only minimal evidence for placing propiconazole in this category [Group C] . . ." This minimal evidence, according to the SAP "is based on the incidence of liver tumors in male mice given the agent at a dose that was excessive (demonstrated by increased mortality in the first year of the study, and increased SGOT, SAP, and SGPT in these animals)".

3. Second Peer Review - Evaluation of the SAP Findings

The HED Peer Review Committee met on March 30, 1988, to examine the issues raised by the SAP with respect to the classification of the carcinogenicity of propiconazole and the need for quantification of the estimated potential human risk.

Upon reconsideration, the Committee still concluded that the data available on the mouse demonstrated sufficient evidence of carcinogenicity in the male mice and, therefore, the Group C classification was appropriate. The Committee based its decision on the following:

a. Administration of propiconazole was associated with a highly significant increase ($p < 0.01$) of benign as well as malignant tumors in male CD1 mice.

b. No evidence of overt toxicity to the liver.

c. Mortality in males of the high-dose group was not dramatically increased, and the increase was limited to the first year of the study.

d. The uncommon biological behavior of these tumors, in that they were considered a contributing factor to death in many male mice at the high dose level and in some cases, the mice were sacrificed because of a distended abdomen due to the underlying liver enlargement caused by the tumors.

e. Structural similarity to homolog etaconazole (associated with liver adenomas and carcinomas in male and female mice), analog Baytan (Group C based on hepatocellular adenomas in female mice), and Bayleton, another triazole fungicide (associated with hepatocellular adenomas in male and female mice).

The Committee took as precedent the SAP's classification of triadimenol (Baytan) as a Group C oncogen based on a marginal increase in liver adenomas in female mice in spite of a dose-related increase in liver enzymes (SGOT, SAP, and SGPT) and liver hyperplasia in that study.

The Committee also considered that a risk assessment using a linearized low-dose extrapolation model in this case was appropriate. The Committee based its decision on the fact that the treatment resulted in a highly significant increase of tumors, increased malignancy, and an accelerated response in these animals. Furthermore, the dose selection and spacing in the mouse study was such that the mid dose of 500 ppm could not provide any information on the carcinogenic response of propiconazole.

4. Third Peer Review - Evaluation of Registrant's Rebuttal

This meeting was called on April 26, 1989 to reconsider the Agency's position regarding the carcinogenicity of propiconazole in light of comments submitted by the registrant, Ciba-Geigy, in a position document entitled "Rationale for using a risk safety factor approach with propiconazole for risk management purposes," received August 30, 1988.

In this position document, the registrant questioned the relevance of the elevated incidence of both benign and malignant tumors in male mice at a dietary level of 2500 ppm which was excessive. The registrant further contended that an adequate dose had been reached at the mid-dose level, i.e., 500 ppm.

With respect to the registrant's question regarding the relevance of the elevated incidence of both benign and malignant tumors in male mice, the Committee believed that this effect was treatment-related for the following reasons:

a. The increase was highly significant ($p < 0.01$), and included increases in malignancy and multiplicity and occurred at an accelerated rate.

b. The uncommon biological behavior and morphology of these tumors, in that the tumors in the high-dose males were larger in size, reported in multiple and progressed in an aggressive manner. These tumors were considered a contributing factor to death. In some cases, the mice had to be sacrificed because of distended abdomens due to the underlying liver enlargement caused by the tumor.

c. Additional data were provided indicating that propiconazole is metabolized in a manner similar to etaconazole, another triazole which has been associated with a significant increase in liver adenomas and carcinomas in both male and female mice.

The Committee recommended that the classification of propiconazole should remain unchanged until further evaluation of individual animal data to ascertain the number of animals with multiple liver cell tumors and the extent of liver enlargement and discoloration in the treatment and control groups.

No official report was issued at that time, and the recommendations of the Committee were conveyed in a brief memorandum to the Fungicide-Herbicide Branch of the Registration Division/OPP. The Committee decided to reconvene at a future date to continue the discussion once the requested information was available.

5. Fourth Peer Review Meeting

The HED Peer Review Committee reconvened to consider further the registrant's arguments that the MTD had been exceeded at the 2500 ppm treatment level. A detailed presentation of the results of a reevaluation of the mouse oncogenicity study was made.

The reevaluation of the study resulted in confirmation of the increased incidence of hepatocellular adenomas and carcinomas in male mice from the 2500 ppm treatment group. The reviewer reemphasized that a marked increase in multiple tumors occurred in this group.

With regard to the increased mortality observed in the high dose males, this argument was not taken as evidence dosing was excessive in that many of the mice were sacrificed moribund or for humane reasons because of the occurrence of large liver tumors. In some cases, the livers were so enlarged due to tumor burden as to result in abdominal distension.

Arguments that the 500 ppm treatment level constituted an adequate top dose were not accepted. None of the criteria for an adequate dosing were achieved at this dose level. The body weight decrement indicated by the registrant as statistically significant was found to not be biologically significant in as much as the difference between body weights for the 500 ppm group and control males was generally only one gram.

The Committee concluded that the classification of propiconazole as a Group C carcinogen with quantification of potential human risk should not be changed on the basis of arguments presented by the registrant.

6. Fifth Peer Review - April, 1992

The registrant has provided an additional submission requesting further consideration of the issue of the MTD for propiconazole in mice. The registrant continues to argue that the high-dose was excessive in the mouse oncogenicity study (Acc. No. 073919, 250784-250786, 251237). They further argue that the data from the high dose (2500 ppm) should not be included in the evaluation of carcinogenic potential of propiconazole.

In support of these arguments, the registrant has provided two subchronic oral toxicity studies in mice in an attempt demonstrate that chronic studies exceeded appropriate dosing to assess carcinogenicity.

Ciba-Geigy also has provided a reread of the pathology slides from the study by J Hardisty, DVM, which they feel indicates sufficient concurrent liver toxicity at 2500 ppm to document that this dose was excessive. These data were not present in the original pathology report by JM Offer, DVM, of

Huntingdon Research Centre. Due to the inconsistency in the reports, Tox Branch requested that an independent (third) evaluation of the slides be made to determine if the pathology reported in Hardisty's report could be confirmed. L Brennecke, DVM, has performed this evaluation which was limited to the control, mid and high dose groups to determine if sufficient toxicity exists to exclude the high dose group.

D. Evaluation of Tumor Data

The registrant has challenged the argument that the tumors produced in the male mice are morphologically different from the background tumors in the control and lower dose mice. This particular discussion arises from the use of difference in morphology as a factor in deciding to quantify the carcinogenic risk from propiconazole.

The PRC determined that, although the adenomas observed in the treated animals were larger and more numerous than those in controls, the tumor type (adenomas) was the same. The numbers of hepatocellular tumors in the control animals was also high. No excessive numbers of tumors were found in female mice.

The statistical evaluation of the incidence of male mouse liver tumors are shown in the following tables. The adenomas were statistically increased by both trend and pair-wise comparison at the high doses ($p<0.01$). The carcinomas were statistically increased by trend analysis, and were increased at the high-dose ($p<0.05$) when the analysis of 2 pathologists were used (26155 or 25155 affected), but not using the analysis of the third pathologist (20154 affected). Statistical analysis of the combined adenomas/carcinomas yielded significant increases ($p<0.01$) for both the trend and pair-wise comparison at the high dose.

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Propiconazole - Male Mouse Study, Hepatocellular Adenoma Only Tumor Rates* and Peto's Prevalence Test Results (p values)

Tumors	Dose (ppm) 0	500	2500
Adenomas Only			
J.M. Offer (%)	13/64 (20)	10[a]/62 (16)	22/56 (39)
p=	0.001**	0.668(n)	0.007**
J. Hardisty (%)	12/64 (19)	13[b]/62 (21)	23/56 (41)
p=	0.000**	0.419	0.001**
L.J. Brennecke (%)	13/64 (20)	12[c]/62 (19)	28/56 (50)
p=	0.000**	0.514(n)	0.000**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

[a] First adenoma observed at week 44, dose 500 ppm.
[b] First adenoma observed at week 44, dose 500 ppm.
[c] First adenoma observed at week 44, dose 500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

Propiconazole - Male Mouse Study, Hepatocellular Carcinoma Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Carcinomas			
Pathologist			
J.M. Offer (%)	15/62 (24)	15/60 (25)	26[a]/55 (47)
p=	0.003**	0.511	0.010*
J. Hardisty (%)	16/62 (26)	13/60 (22)	25[b]/55 (45)
p=	0.006**	0.75(n)	0.035*
L.J. Brennecke (%)	14/60 (23)	11/58 (19)	20[c]/54 (37)
p=	0.028*	0.801(n)	0.050

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first carcinoma.

n Negative change from control.

[a] First carcinoma observed at week 50, dose 2500 ppm.
[b] First carcinoma observed at week 50, dose 2500 ppm.
[c] First carcinoma observed at week 53, dose 2500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Propiconazole - Male Mouse Study, Hepatocellular Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
Tumors Combined (Adenoma &/or Carcinoma)	0	500	2500
Pathologist			
J.M. Offer	28/63	25/62	48/56
(%)	(44)	(40)	(86)
p=	0.000**	0.702(n)	0.000**
J. Hardisty	28/63	26/61	48/56
(%)	(44)	(43)	(86)
p=	0.000**	0.693(n)	0.000**
L.J. Brennecke (%)	27/63	23/62	48/56
	(43)	(37)	(86)
p=	0.000**	0.718(n)	0.000**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

E. Evaluation of Supportive Data

1. Subchronic Toxicity Studies

Subchronic Dietary Toxicity Study with CGA-64250 in Mice. MRID 420505-01. RF Potrepka and JC Turnier. Ciba-Geigy Corp., Farmington CN. April 30, 1991.

Groups of 20 male and 20 female Crl:CD-1 (ICR) BR (Swiss) mice were given 0, 20, 500, or 2500 ppm propiconazole in the diet for 17 weeks. An additional two groups of 20 males each were given diet containing 850 or 1450 ppm. Mice were seven weeks old at the initiation of the study.

No effect on body weight gain was reported. No treatment related mortality or toxic signs were reported.

Treatment related increases in ALT/SGPT were reported for males receiving ≥850 ppm and females given 2500 ppm. High dose females also had increased levels of AST/SGOT. Cholesterol levels were decreased in males receiving ≥850 ppm (Table 1).

Significantly increased liver weights (absolute, relative to body weight and relative to brain weight) were reported in males at treatment levels ≥500 ppm and in females given 2500 ppm (Table 2). Increased weights were accompanied by increased evidence of histopathological lesions which exhibited a dose related increase in both frequency and severity (Table 3). At 500 and 850 ppm, all diagnosed hypertrophy in the males was mild; moderate hypertrophy was present in 9/20 and 18/20 animals in the 1450 and 2500 ppm groups, respectively. In high dose females, 14/20 had minimal to mild hypertrophy while 3/20 were classified as moderate. Necrosis was present in males receiving ≥500 ppm and increased in frequency and severity with increasing dose. It occurred as scattered individual cell foci and/or multicellular areas. Severity at all doses was minimal to mild. Significant vacuolation occurred only in high dose males. The severity rating was minimal in 2/20, mild in 7/20 and moderate in 1/20 animals.

Based on these findings, the PRC determined that the 1450 and 2500 dose levels were very toxic, and that the MTD was 850 ppm.

Table 1: Clinical Chemistry Findings

Analyte (units)	Week of Study	Dose Level (ppm) 0	20	500	850	1450	2500
Male							
Cholesterol (mg/dl)	13	120	108	121	108	70**	71**
	17	119	104	105	91**	66**	67**
Alanine Amino-transferase (U/l)	13	52	31	39	43	65	81
	17	17	33	28	29	65**	128**
Female							
Aspartate Amino-transferase (U/l)	13	67	60	61	---	---	68
	17	45	47	55	---	---	68**
Alanine Amino-Transferase (U/l)	13	27	24	27	---	---	64**
	17	17	20	21	---	---	61**

** $p < 0.01$

Table 2: Absolute and relative liver weights of male and female mice

Dose Level (ppm)	Absolute (g)	% of Body Weight	% of Brain Weight
Male			
0	1.445	3.961	286.3
20	1.408	4.108	283.8
500	1.660*	4.486**	332.2*
850	1.792**	5.131**	363.0**
1450	2.450**	6.701**	480.2**
2500	2.773**	8.102**	555.0**
Female			
0	1.177	4.182	230.6
20	1.267	4.533	250.9
500	1.215	4.414	243.9
2500	2.110**	7.684**	435.5**

* $p < 0.05$, ** $p < 0.01$

Table 3: Incidence of Histopathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Male						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	4	14**	20**	20**
Necrosis	1	0	2	4	8*	12**
Individual Cell	0	0	0	0	2	12**
Total Affected	1	0	2	4	10**	18**
Vacuolation	0	0	6*	2	3	10**
Individual Cell	0	0	0	0	0	6**
Total Affected	0	0	6*	2	3	16**
Female						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	0	---	---	17**
Necrosis	0	0	0	---	---	6*
Individual Cell	0	0	0			1
Total Affected	0	0	0			6*
Vacuolation	0	0	0	---	---	2
Individual Cell	0	0	0			1
Total Affected	0	0	0			3

* $p < 0.05$, ** $p < 0.01$

13-Week Toxicity Study with CGA-64250 in Male Mice. MRID 420505-02. RF Potrepka and JC Turnier. Ciba-Geigy Corp., Farmington, CN. April 30, 1991.

Groups of 40 male Crl:CD-1 (ICR) BR (Swiss) mice were given 0, 20, 500, 850, 1450, or 2500 ppm propiconazole in diet. They were 37 days old at initiation of the study. Ten animals from each group were sacrificed at 4 and 8 weeks. The remaining 20 mice from each group were sacrificed at 13 weeks. No unscheduled deaths or toxic signs were reported during this study. A slight body weight decrement was reported for the 2500 ppm treatment group, with a difference of about 1 gram at week 8. No further difference was reported. At week 8, the 2500 ppm group had gained 0.9 g less than the control group. However, no further change occurred during the study.

Mice exhibited significantly decreased cholesterol levels at treatment levels ≥850 ppm (Table 4). This response to treatment was dose related. ALT/SGPT and sorbitol dehydrogenase were increased in a dose related manner at treatment levels ≥850 ppm. None of the effects reported exhibited a time related change. Differences were established by Week 4 and persisted until the Week 13 sacrifice.

Table 4: Clinical Chemistry Findings

Parameter (units)	Week of Study	Dose Level (ppm)			
		0	850	1450	2500
Cholesterol (mg/dl)	4	129	92**	81**	47**
	8	114	104	58**	57**
	13	122	86**	75**	67**
Alanine Amino transferase (U/l)	4	24	42	56**	86**
	8	24	30	53**	74**
	13	22	35	53**	79**
Sorbitol Dehydrogenase (U/l)	4	26	45*	58**	66**
	8	27	30	47**	5[illegible]**
	13	22	31*	45**	58**

** $p<0.01$

Absolute and relative liver weights were increased in a dose related manner in treatment groups receiving feed containing ≥500 ppm (Table 5). At necropsy, increased prominence in the lobular architecture was reported in the 1450 and 2500 ppm treatment groups. Incidence increased with duration of treatment.

Table 5: Absolute and relative liver weights

Dose Level (ppm)	Absolute (g)	% of Body Weight	% of Brain Weight
0	1.307	4.524	266.7
20	1.194	4.335	251.1
500	1.523*	5.339**	317.8
850	1.709**	6.078**	356.5**
1450	1.984**	7.043**	414.5**
2500	2.382**	8.776**	512.0**

* $p < 0.05$, ** $p < 0.01$

A dose related increase in both the incidence and severity of hypertrophy, necrosis and vacuolation was reported, beginning with the 500 ppm treatment group (Table 6). Hypertrophy was graded as mild to moderate with the more severe lesions occurring at the 1450 and 2500 ppm dose levels. Necrosis was either single cell foci or multiple cell clusters. Necrosis and vacuolation were graded from minimal to moderate with the more severe effects at higher doses. In addition, the frequency and severity increased with increasing time on treatment. Based on these findings, the MTD appears to be 850 ppm.

2. Reevaluation of Histopathology Slides

Two reevaluations of the slides from the original study have been conducted. The initial reevaluation was conducted by Jerry Hardisty, DVM, of Experimental Pathology Laboratories, Inc. (Reexamination of the Liver Tumor Response in Male and Female Mice - Pathology Report, May 6, 1991). This evaluation was commissioned by Ciba-Geigy Corp. The purpose of this submission was to present evidence that excessive nonneoplastic lesions were present in the livers of male mice given 2500 ppm propiconazole in the diet for two years. These data were accompanied by arguments from the registrant that the original pathology report from Huntingdon Research Centre (HRC Report No. CBG/196/81827) understated the extent of concurrent nonneoplastic lesions, thereby causing misinterpretation of the data. They argued that the Hardisty evaluation was more correct and indicates that the 2500 ppm treatment level clearly exceeded the MTD.

Another re-evaluation of the slides was commissioned by HED to validate the report from EPL. This evaluation included only the livers from the control, 500 ppm and 2500 ppm male mice, those slides which reflect the questionable setting of the MTD. This evaluation was conducted by Lucas H. Brennecke, DVM, of Pathology Associates, Inc. (Histopathologic Review of Livers in Male Mice From the Long-Term Feeding Study in Mice With CGA 64 250 (Propiconazole), January 30, 1992).

As an initial evaluation of the similarity of the evaluations from JM Offer (HRC), J Hardisty (EPL) and L Brennecke (PAI), Bernice Fisher conducted a tumor rate analysis using Peto's Prevalence tests of trends and pair-wise comparison of controls and each dose level for each set of data from each pathologist (See attached memo). The increase in total hepatocellular tumors was essentially identical with respect to trends and pair-wise comparison to control for all three evaluations. All three evaluations indicated significant trend for hepatocellular carcinomas with treatment.

Table 6: Incidence of Histopathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Interval Period: 4 Weeks						
Total Livers Examined	10	10	10	10	10	10
Hypertrophy	0	0	2	6**	10**	10**
Necrosis	1	0	0	4	3	6
Individual Cell	0	0	1	0	5*	4
Total Affected	1	0	0	4	7*	7*
Vacuolation	0	0	0	0	1	6**
Individual Cell	0	0	0	0	1	2
Total Affected	0	0	0	0	2	8**
Interval Period: 8 weeks						
Total Livers Examined	10	10	10	10	10	10
Hypertrophy	0	0	5*	9**	10**	10**
Necrosis	0	0	2	2	4	6**
Individual Cell	0	0	0	0	8**	9**
Total Affected	0	0	2	2	9**	9**
Vacuolation	0	0	1	0	4	4
Individual Cell	0	0	0	0	0	7
Total Affected	0	0	1	0	4	7**
Interval Period: 13 weeks						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	3	20**	20**	20**
Necrosis	0	0	1	2	9**	5*
Individual Cell	0	0	0	1	10**	16**
Total Affected	0	0	1	3	15**	18**
Vacuolation	0	1	1	5*	6*	6*
Individual Cell	0	0	0	0	3	18
Total Affected	0	1	1	5*	9**	6**
Mineralization	0	0	0	2	0	6*

* $p < 0.05$, ** $p < 0.01$

Two of three evaluations (Offer and Hardisty) indicated significant pair-wise comparisons to the control, while the third (Brenneke) indicated borderline significance for increases in carcinomas. Comparison of the statistical analysis of hepatocellular adenomas also indicated the same significant results with increasing trends and significant pair-wise comparisons of the high dose to the controls. Although there was some difference in tumor count, this did not differentially affect the statistical results among the pathologists. Based upon the total tumor analysis, there is no evidence that the new pathology report would indicate a need for recalculation of the Q_1*.

With respect to the question of morphology of hepatocellular adenomas in the 2500 ppm treatment group, no difference was found with respect to tumor type relative to the lower dose groups and the controls. The difference in the high dose group was rather increased numbers and size of tumors of the same types seen in the controls.

With respect to nonneoplastic lesions, effects reported by Hardisty and Brennecke were similar (Table 7). A dose related increase in incidence and severity of hepatocyte enlargement was reported by both pathologists beginning with the 500 ppm treatment level. In addition, eosinophilic foci were increased at 500 ppm. No other nonneoplastic effects were reported at this treatment level. In the 2500 ppm treatment group, the severity and incidence of hepatocyte vacuolation, chronic inflammation and pigmented Kupffer cells was increased. Effects in the high dose group were limited in severity to moderately severe for hepatocyte enlargement and chronic inflammation, and moderate for pigmented Kupffer cells and hepatocyte vacuolation. No other treatment related effects were reported. Hepatocyte necrosis in all dose groups was comparable to the control.

Table 7: Incidence of Histopathological Lesions in the Livers of Male Mice - Terminal Sacrifice and Early Deaths

Lesion	Dose Level (ppm)			
	0	100	500	2300
Total Livers Examined*	53 (53)	53 (0)	51 (53)	55 (55)
Eosinophilic Focus	1 (1)	1 (-)	5 (4)	6 (17)
Hepatocyte Enlargement	12 (20)	6 (-)	31 (30)	45 (49)
Minimal	4 (9)	3 (-)	15 (11)	0 (7)
Mild	7 (8)	3 (-)	14(13)	18 (11)
Moderate	1 (3)	0 (-)	2 (6)	26 (28)
Moderately Severe	0 (0)	0 (-)	0 (0)	1 (3)
Hepatocyte Vacuolation	7 (5)	5 (-)	7 (5)	19 (30)
Minimal	4 (3)	3 (-)	5 (0)	8 (10)
Mild	3 (1)	2 (-)	2 (4)	11 (16)
Moderate	0 (1)	0 (-)	0 (1)	0 (4)
Inflammation, Chronic	30 (28)	26 (-)	26 (29)	38 (41)
Minimal	12 (15)	11 (-)	17 (21)	11 (22)
Mild	13 (10)	9 (-)	6 (6)	14 (16)
Moderate	5 (3)	6 (-)	3 (2)	12 (3)
Moderately Severe	0 (0)	0 (-)	0 (0)	1 (0)
Pigmented Kupffer Cells	7 (3)	8 (-)	8 (2)	37 (33)
Minimal	7 (3)	6 (-)	8 (2)	7 (11)
Mild	0 (0)	2 (-)	0 (0)	22 (20)
Moderate	0 (0)	0 (-)	0 (0)	8 (2)

*Pathologist = Hardisty (Brennecke)

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on propiconazole in a weight-of-the-evidence determination of carcinogenic potential.

Increased numbers of adenomas (increased trend and pairwise comparision, $p<0.01$) were found in the livers of male CD1 mice given 2500 ppm of propiconazole in the diet. The treated animals also had earlier fatalities than the controls. The numbers of carcinomas also were increased (increased trend, $p<0.05$).

Although the adenomas observed in the treated animals were larger and more numerous than those in controls, the tumor type (adenomas) was the same. The numbers of hepatocellular tumors in the control animals also was high. No excessive numbers of tumors were found in female mice.

The Peer Review Committee determined that the high dose used in this study was excessively toxic but that the other doses were not adequate for assessing the carcinogenic potential of propiconazole. The 2500 ppm used in the two year chronic study exceeded the MTD demonstrated in the 90 day study based on the endpoint of hepatic necrosis. The 500 ppm used in the chronic study was inadequate to assess the carcinogenicity of propiconazole.

In a rat study conducted with acceptable doses of propiconazole, no excessive numbers of tumors were found.

Propiconazole is structurally related to other systemic triazole fungicides which are known to be carcinogenic.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that the classification for propiconazole should be Group C - possible human carcinogen, based on the finding of increased numbers of adenomas ($p<0.01$ by pairwise comparison at the high dose) in the livers of male mice. The numbers of carcinomas were also increased using the trend analysis ($p<0.05$). The treated animals also had earlier fatalities than the controls.

For the purpose of risk characterization the Peer Review Committee recommended that the Reference Dose approach should be used for quantification of human risk (RfD). This decision was based on the new data submitted (90 day studies) which showed excessive toxicity at the high dose (2500 ppm); however, the middle dose (500 ppm) was not considered sufficiently high for assessing the carcinogenic potential of propiconazole. Therefore, there are no appropriate data for the calculation of a q1*.

The Peer Review Committee discussed the need to repeat the mouse study using adequate doses. This decision, however, was deferred to the HED Re-registration data review panel.

ATTACHMENT

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Propiconazole, Male Mouse Dietary Study - Comparisons Among Pathologists - J.M. Offer, J. Hardisty and L.H. Brennecke of Hepatocellular Tumor Rates

Caswell no.323EE

From: Bernice Fisher, Biostatistician Bernice Fisher 3/30/9
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

To: Elizabeth Doyle, Ph.D., Section Head
Review Section IV
Herbicide/Fungicide/Antimicrobial Support Branch
Health Effects Division (H7509C)

Thru: Kerry L. Dearfield, Ph.D., Acting Section Head
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

Dr. Doyle requested a comparison of 3 pathologist's (J.M. Offer, J. Hardisty and L.H. Brennnecke) observation of the number of hepatocellular tumors that occurred in the 2-year dietary study of propiconazole (CGA 64 250) in male mice.

Since only 0, 500 and 2500 ppm dose level tumors were re-evaluated by L.H. Brennecke, the statistical analysis of the comparative data from the 3 pathologists was based only on these dose levels (original study had an additional dose of 100 ppm).

Male rat survival in the propiconazole study was significantly decreased according to the trend analysis of mortality with incremental doses of propiconazole (Table 1).

Therefore tumor rate analysis was based on Peto's Prevalence tests of trends and pair-wise comparison of controls and each dose level for each set of data from each pathologist.

The comparison of combined (adenoma and/or carcinoma) hepatocellular tumor rates in terms of the statistical findings produced the same significant (significant increase in trend and significant increase in pair-wise comparison of controls and the highest dose) among all 3 pathologists. The summary of hepatocellular tumors observed in the high dose was exactly the same for all pathologists. The control data for 2 of them was the same and the other one observed one more tumor. In the 500 ppm group the number of tumors observed were 26, 25 and 23 (Table 2).

The comparison of hepatocellular carcinoma tumor rates among the 3 pathologists indicated that the statistical analysis of the data resulted in a significant increasing dose related trend in all 3 data sets. Two out of the evaluated data sets also had a significant increase in the pair-wise comparison of controls and the highest(2500 ppm) dose group. The analysis of the other observed data set resulted in a borderline significant difference in the same pair-wise comparison. The number of carcinomas observed were 26, 25 and 20 in the highest dose group among the 3 pathologists (Table 3).

The comparison of the statistical analysis of hepatocellular adenomas only also indicated the same significant results (increasing trend and pair-wise comparison of controls and the highest dose group) among the data from the 3 pathologists. There was some variation in the number of adenomas only (22, 23 and 28) observed in the highest dose group. However these differences did not differentially affect the statistical results among the pathologists (Table 4).

Table 1. Propiconazole - Mouse Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53[a]	53-78	79-104[b]	Total
0	0/64	2/64	11/62	11/51	16/40	29/53(55)**
500	1/64	5/63	11/58	10/47	16/37	32/53(60)*
2500	5/64	5/59	9/54	16/45	15/29	41/55(75)*

+ Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 53.

[b] Final sacrifice at weeks 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 2. Propiconazole - Male Mouse Study, Hepatocellular Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
Tumors Combined (Adenoma &/or Carcinoma)	0	500	2500
Pathologist			
J.M. Offer	28/63	25/62	48/56
(%)	(44)	(40)	(86)
p=	0.000**	0.702(n)	0.000**
J. Hardisty	28/63	26/61	48/56
(%)	(44)	(43)	(86)
p=	0.000**	0.693(n)	0.000**
L.J. Brennecke (%)	27/63	23/62	48/56
	(43)	(37)	(86)
p=	0.000**	0.718(n)	0.000**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

Table 3. Propiconazole - Male Mouse Study, Hepatocellular Carcinoma Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Carcinomas			
Pathologist			
J.M. Offer (%)	15/62 (24)	15/60 (25)	26[a]/55 (47)
p=	0.003**	0.511	0.010*
J. Hardisty (%)	16/62 (26)	13/60 (22)	25[b]/55 (45)
p=	0.006**	0.75(n)	0.035*
L.J. Brennecke (%)	14/60 (23)	11/58 (19)	20[c]/54 (37)
p=	0.028*	0.801(n)	0.050

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first carcinoma.

n Negative change from control.

[a] First carcinoma observed at week 50, dose 2500 ppm.
[b] First carcinoma observed at week 50, dose 2500 ppm.
[c] First carcinoma observed at week 53, dose 2500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

Table 4. Propiconazole - Male Mouse Study, Hepatocellular Adenoma Only Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Adenomas Only			
J.M. Offer (%)	13/64 (20)	10[a]/62 (16)	22/56 (39)
p=	0.001**	0.668(n)	0.007**
J. Hardisty (%)	12/64 (19)	13[b]/62 (21)	23/56 (41)
p=	0.000**	0.419	0.001**
L.J. Brennecke (%)	13/64 (20)	12[c]/62 (19)	28/56 (50)
p=	0.000**	0.514(n)	0.000**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

[a] First adenoma observed at week 44, dose 500 ppm.
[b] First adenoma observed at week 44, dose 500 ppm.
[c] First adenoma observed at week 44, dose 500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

References

Armitage, P. (1955) Tests for Linear Trends in Proportions, Biometrics 11, 375-386.

Cochran, W.G. (1954) Some Methods for Strengthening the Comon X^2 Test, Biometrics 10, 417-451.

Cox, D.R. (1972) Regression Models and Life Tables (with discussion) J. Royal Stat. Soc. Ser. B. 34, 187-220.

Thomas, D.G., Breslow, N., and Gart, J.J. (1977) Trend and Homogeneity Analysis of Proportions and Life Life Table Data, Computers and Biomedical Research 10, 373-381.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FILE COPY

April 1, 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review Meeting on
(54) **PROPICONAZOLE AND DICOFOL**

FROM: Esther Rinde, Ph.D. E.R.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509c)

TO: Addressees

Attached for your review are packages on **Propiconazole and Dicofol** prepared by **Drs. E. Doyle and W. Phang.**

A meeting to consider the carcinogenicity classification of these two chemicals is scheduled for **Wednesday April 15, 1992, at 10:00 am in Room 813, CM2** (*Propiconazole will be discussed from 10:00 am to 11:00 am and the discussion of Dicofol will follow from 11:00 am to 12:00 pm*).

Addressees

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
R. Beliles
K. Baetcke
L. Brennecke
M. Van Gemert
M. Copley
K. Dearfield
J. Parker
H. Pettigrew
W. Sette
G. Ghali
B. Fisher
J. Du
Y. Woo
J. Quest
E. Saito (for microfiche-with one-liner)
A. Clevenger
E. Andersen
E. Doyle
W. Phang J. Rowe

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WASHINGTON, D.C. 20460

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Peer Review of Propiconazole (5TH)

FROM: Elizabeth A. Doyle, Ph.D., Section Head
Review Section IV, Tox Branch II (H7509C)

E. A. Doyle
3/31/92

TO: Esther Rinde, Ph.D.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509C)

THRU: Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C)

Marcia van Gemert
4/1/92

Attached is the peer review package for the fifth evaluation of Propiconazole. Included with the package are two (2) DER's and a statistical analysis by Bernice Fisher.

3. Second Peer Review - Evaluation of the SAP Findings

The HED Peer Review Committee met on March 30, 1988, to examine the issues raised by the SAP with respect to the classification of the carcinogenicity of propiconazole and the need for quantification of the estimated potential human risk.

Upon reconsideration, the Committee still concluded that the data available on the mouse demonstrate sufficient evidence of oncogenicity in the male mice and, therefore, the Group C classification is appropriate. The Committee based its decision on the following:

a. Administration of propiconazole was associated with a highly significant increase ($p < 0.01$) of benign as well as malignant tumors in male CD1 mice.

b. No evidence of overt toxicity to the liver.

c. Mortality in males of the high-dose group was not dramatically increased, and the increase was limited to the first year of the study.

d. The uncommon biological behavior of these tumors, in that they were considered a contributing factor to death in many male mice at the high dose level and in some cases, the mice were sacrificed because of a distended abdomen due to the underlying liver enlargement caused by the tumors.

e. Structural similarity to homolog etaconazole (associated with liver adenomas and carcinomas in male and female mice), analog Baytan (Group C based on hepatocellular adenomas in female mice), and Bayleton, another triazole fungicide (associated with hepatocellular adenomas in male and female mice).

The Committee took as precedent the SAP's classification of triadimenol (Baytan) as a Group C oncogen based on a marginal increase in liver adenomas in female mice in spite of a dose-related increase in liver enzymes (SGOT, SAP, and SGPT) and liver hyperplasia in that study.

The Committee also considered that a quantitative risk assessment in this case is appropriate. The Committee based its decision on the fact that the treatment resulted in a highly significant increase of tumors, increased malignancy, and an accelerated response in these animals. Furthermore the dose selection and spacing in the mouse study was such that the mid dose of 500 ppm could not provide any information on the oncogenic response of propiconazole.

4. Third Peer Review - Evaluation of Registrant's Rebuttal

This meeting was called on April 26, 1989 to reconsider the Agency's position regarding the carcinogenicity of propiconazole in

The reevaluation of the study resulted in confirmation of the increased incidence of hepatocellular adenomas and carcinomas in male mice from the 2500 ppm treatment group. The reviewer reemphasized that a marked increase in multiple tumors occurred in this group.

With regard to the increased mortality observed in the high dose males, this argument was not taken as evidence of exceeding the MTD in that many of the mice were sacrificed moribund or for humane reasons because of the occurrence of large liver tumors. In some cases, the livers were so enlarged due to tumor burden as to result in abdominal distension.

Arguments that the 500 ppm treatment level constituted the MTD were not accepted. None of the criteria for an MTD were achieved at this dose level. The body weight decrement indicated by the registrant as statistically significant was found to be not biologically significant in as much as the difference between body weights for the 500 ppm group and control males was generally one gram.

The Committee concluded that the classification of propiconazole as a Group C oncogen with quantification of potential human risk, should not be changed on the basis of arguments presented by the registrant.

6. Fifth Peer Review - Present

The registrant has provided an additional submission requesting further consideration of the issue of the MTD for propiconazole in mice. The registrant continues to argue that the MTD was exceeded in the mouse oncogenicity study (Acc. No. 073919, 250784-250786, 251237). They further argue that the data from the high dose (2500 ppm) should not be included in the evaluation of oncogenic potential of propiconazole.

In support of these arguments, the registrant has provided two subchronic oral toxicity studies in mice to in an attempt demonstrate that the MTD was exceeded.

Ciba-Geigy has also provided a reread of the pathology slides from the study by J Hardisty, DVM which they feel indicates sufficient concurrent liver toxicity at 2500 ppm to document that the MTD was exceeded. These data were not present in the original pathology report by JM Offer, DVM of Huntingdon Research Centre. Due to the inconsistency in the reports Tox Branch requested that an independent third evaluation of the slides be made to determine if the pathology reported in Hardisty's report could be confirmed. L Brennecke, DVM has performed this evaluation, limited to the control, mid and high dose groups to determine if sufficient toxicity exists to eliminate the high dose group.

The registrant has challenged the argument that the tumors produced in the male mice are morphologically different than the background

Table 1: Clinical Chemistry Findings

Analyte (units)	Week of Study	Dose Level (ppm) 0	20	500	850	1450	2500
Male							
Cholesterol (mg/dl)	13	120	108	121	108	70**	71**
	17	119	104	105	91**	66**	67**
Alanine Amino-transferase (U/l)	13	52	31	39	43	65	81
	17	17	33	28	29	65**	128**
Female							
Aspartate Amino-transferase (U/l)	13	67	60	61	---	---	68
	17	45	47	55	---	---	68**
Alanine Amino-Transferase (U/l)	13	27	24	27	---	---	64**
	17	17	20	21	---	---	61**

** $p < 0.01$

Table 3: Incidence of Histopathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Male						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	4	14**	20**	20**
Necrosis	1	0	2	4	8*	12**
Individual Cell	0	0	0	0	2	12**
Total Affected	1	0	2	4	10**	18**
Vacuolation	0	0	6*	2	3	10**
Individual Cell	0	0	0	0	0	6**
Total Affected	0	0	6*	2	3	16**
Female						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	0	---	---	17**
Necrosis	0	0	0	---	---	6*
Individual Cell	0	0	0			1
Total Affected	0	0	0			6*
Vacuolation	0	0	0	---	---	2
Individual Cell	0	0	0			1
Total Affected	0	0	0			3

* $p < 0.05$, ** $p < 0.01$

Although treatment related effects on the liver were reported, the treatment levels selected appeared to be well tolerated by the mice. Therefore, this study was not accepted as evidence that the 2500 ppm treatment level is in excess of the MTD.

13-Week Toxicity Study with CGA-64250 in Male Mice. MRID 420505-02. RF Potrepka and JC Turnier. Ciba-Geigy Corp., Farmington, CN. April 30, 1991.

Groups of 40 male Crl:CD-1 (ICR) BR (Swiss) mice were given 0, 20, 500, 850, 1450, or 2500 ppm propiconazole in diet. They were 37 days old at initiation of the study. Ten animals from each group were sacrificed at 4 and 8 weeks. The remaining 20 mice from each group were sacrificed at 13 weeks. No unscheduled deaths or toxic signs were reported during this study. A slight body weight decrement was reported for the 2500 ppm treatment group, with a difference of about 1 gram at week 8. No further difference was reported. At week 8, the 2500 ppm group had gained 0.9 g less than the control group. However, no further change occurred during the study.

A dose related increase in both the incidence and severity of hypertrophy, necrosis and vacuolation was reported, beginning with the 500 ppm treatment group. Hypertrophy was graded as mild to moderate with the more severe lesions occurring at the 1450 and 2500 ppm dose levels. Necrosis was either single cell foci or multiple cell clusters. Necrosis and vacuolation were graded from minimal to moderate with the more severe effects at higher doses. In addition, the frequency and severity increased with increasing time on treatment.

Although treatment related effects on the liver were reported, the treatment levels selected appeared to be well tolerated by the mice. Therefore, this study was not accepted as evidence that the 2500 ppm treatment level is in excess of the MTD.

2. Reevaluation of Histopathology Slides

Two reevaluations of the slides from the original study have been conducted. The initial reevaluation was conducted by Jerry Hardisty, DVM, of Experimental Pathology Laboratories, Inc. (Reexamination of the Liver Tumor Response in Male and Female Mice - Pathology Report, May 6, 1991). This evaluation was commissioned by Ciba-Geigy Corp. The purpose of this submission was to present evidence that excessive nonneoplastic lesions were present in the livers of male mice given 2500 ppm propiconazole in diet for two years. These data were accompanied by arguments from the registrant that the original pathology report from Huntingdon Research Centre (HRC Report No. CBG/196/81827) understated the extent of concurrent nonneoplastic lesions, thereby causing misinterpretation of the data. They argue that the Hardisty evaluation is more correct and indicates that the 2500 ppm treatment level clearly exceeded the MTD.

Due to the inability of this reviewer to resolve the issue, another evaluation of the slides was commissioned by HED to validate the report from EPL. This evaluation included only the livers from the control, 500 ppm and 2500 ppm male mice, those slides which reflect the questionable setting of the MTD. This evaluation was conducted by Lucas H. Brennecke, DVM, of Pathology Associates, Inc. (Histopathologic Review of Livers in Male Mice From the Long-Term Feeding Study in Mice With CGA 64 250 (Propiconazole), January 30, 1992).

As an initial evaluation of the similarity of the evaluations from JM Offer (HRC), J Hardisty (EPL) and L Brennecke (PAI), Bernice Fisher conducted a tumor rate analysis using Peto's Prevalence tests of trends and pair-wise comparison of controls and each dose level for each set of data from each pathologist (See attached memo). The increase in total hepatocellular tumors was essentially identical with respect to trends and pair-wise comparison to control for all three evaluations. All three evaluations indicated significant trend for hepatocellular carcinomas with treatment.

high dose to the controls. Although there was some difference in tumor count, this did not differentially affect the statistical results among the pathologists. Based upon the total tumor analysis, there is no evidence that the new pathology report would indicate a need for recalculation of the Q_1*.

With respect to the question of morphology of hepatocellular tumors in the 2500 ppm treatment group, no difference was found by either pathologist with respect to tumor type relative to the lower dose groups and the controls. The difference in the high dose group was rather increased numbers and size of tumors of the same types seen in the controls.

With respect to nonneoplastic lesions, effects reported by Hardisty and Brennecke were similar (Table 7). A dose related increase in incidence and severity of hepatocyte enlargement was reported by both pathologists beginning with the 500 ppm treatment level. In addition, eosinophilic foci were increased at 500 ppm. No other nonneoplastic effects were reported at this treatment level. In the 2500 ppm treatment group, the severity and incidence of hepatocyte vacuolation, chronic inflammation and pigmented Kupffer cells was increased. Effects in the high dose group were limited in severity to moderately severe for hepatocyte enlargement and chronic inflammation, and moderate for pigmented Kupffer cells and hepatocyte vacuolation. No other treatment related effects were reported. Hepatocyte necrosis in the all dose groups was comparable to the control.

E. Weight of Evidence Considerations

The Committee is asked the consider the following questions with regard to the oncogenicity of propiconazole:

1) Was the 2500 ppm treatment level in excess of the MTD?

2) Were liver tumors reported in high dose males in the mouse oncogenicity study different morphologically than the tumors in the control animals?

3) Is quantitation of risk for propiconazole appropriate?

009119

Reviewed by: Robert F. Fricke, Ph.D.
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Elizabeth A. Doyle, Ph.D.
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 90-day oral - Mouse (82-1) TOX. CHEM. NO.: 323EE

MRID NO.: 420505-01

TEST MATERIAL: Propiconazole

SYNONYMS: CGA-64250

STUDY NUMBER: F-00098

SPONSOR: Ciba-Geigy Corp., Agricultural Division
P.O. Box 18300, Greensboro, NC 27419

TESTING FACILITY: Ciba-Geigy Corp., Environmental Health Center
400 Farmington Avenue, Farmington, CN 06032

TITLE OF REPORT: Subchronic Dietary Toxicity Study with CGA-64250 in Mice

AUTHOR: Robert F. Potrepka and John C. Turnier

REPORT ISSUED: April 30, 1991

CONCLUSIONS: For 17 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively) for males and 0, 20, 500, or 2500 ppm (equivalent to 3.4, 85 or 434 mg/kg/day, respectively) for females.

	NOEL	LOEL
Male	20 ppm (LDT)	500 ppm (MDT1)
Female	20 ppm (LDT)	2500 ppm (HDT)

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

5. Quality assurance was documented by signed and dated GLP and quality assurance statements.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of toxicity, moribundity and mortality.

a. Toxicity: There were no clinical observations attributable to the administration of the test article.

b. Mortality (survival): One male mouse in the 20 ppm group was found dead during week 15 and one unscheduled sacrifice occurred for a male mouse at 850 ppm during week 10. No female mice died during the study.

2. Body weight: Animals were weighed weekly during the 17 week treatment period.

Results: The body weights of the male and female mice were not significantly different from control values throughout the entire study.

Significant findings for body weight gain in male mice are summarized in Table 2, below. Significant differences were noted only during the first two weeks of the study. The female mice did not show any significant differences between the treated groups and the control.

Table 2: Body Weight Gain (g) for Male Mice

Week of Study	Dose Level (ppm)					
	0	20	500	850	1450	2500
1	0.8	1.1	1.0	0.8	1.2	0.0**
2	0.5	1.1*	1.2*	1.5*	1.4**	1.6

* $p < 0.05$, ** $p < 0.01$

3. Food consumption and compound intake: Food consumption was determined weekly and mean daily consumption was calculated.

a. Food consumption results: Daily food consumption (g/animal/day) was determined for both male and female mice. The females did not show any significant treatment-related effects. Significant findings for the male mice are summarized in Table 3, below.

c. Compound intake results: The average daily compound consumption for male and female animals is summarized below in Table 5.

Table 5: Average daily consumption of compound at each dose level for male and female mice.

Dose Level (ppm)	Compound Consumption (mg/kg/day)	
	Male	Female
20	2.7	3.4
500	65	85
850	112	---
1450	194	---
2500	352	434

4. Ophthalmological examinations: Examinations were performed on all animals at the termination of the study. No treatment-related eye lesions were observed.

5. Hematology and Clinical Chemistry: Clinical chemistry analyses were performed after 13 weeks of exposure and at the termination of the study. The checked (X) parameters were examined.

a. Hematology: Not performed

b. Clinical Chemistry

Electrolytes
- Calcium
- Chloride
- Magnesium
- Phosphorous
- Potassium
- Sodium

Enzymes
- X Alkaline phosphatase
- Cholinesterase
- Creatinine phosphokinase
- Lactic acid dehydrogenase
- X Serum alanine aminotransferase (SGPT/ALT)
- X Serum aspartate aminotransferase (SGOT/AST)

Other
- Albumin
- Blood creatinine
- Blood urea nitrogen
- X Cholesterol
- Globulins
- Glucose
- Total Bilirubin
- Triglycerides
- Total Protein

Results: Significant clinical chemistry findings are shown in Table 6, below.

increases were found in the male animals at 500 ppm or higher and in the female mice at the 2500 ppm.

Table 7: Absolute and relative liver weights of male and female mice

Dose Level (ppm)	Absolute (g)	% of Body Weight	% of Brain Weight
Male			
0	1.445	3.961	286.3
20	1.408	4.108	283.8
500	1.660*	4.486**	332.2*
850	1.792**	5.131**	363.0**
1450	2.450**	6.701**	480.2**
2500	2.773**	8.102**	555.0**
Female			
0	1.177	4.182	230.6
20	1.267	4.533	250.9
500	1.215	4.414	243.9
2500	2.110**	7.684**	435.5**

* $p < 0.05$, ** $p < 0.01$

b. Gross pathology: The only observations of toxicological significance were generalized enlargement and focal discoloration of the livers. The incidence data is presented in Table 8, below.

c. Microscopic pathology

1) Non-neoplastic: Examination of the livers of the male and female mice showed an increased incidence of histopathological lesions (Table 7, below). Male mice showed a dose-related increase in both the incidence and severity of the histopathological lesions, while the females showed significant increases only at 2500 ppm. At 500 and 850 ppm dose levels, all diagnosed hypertrophy in the males was mild; moderate hypertrophy was present in 9/20 and 18/20 for animals in the 1450 and 2500 ppm groups, respectively. In females, 14/20 showed minimal to mild hypertrophy, while 3/20 were classified as moderate.

Table 8: Incidence Data for Gross Pathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Male						
Enlargement	1/20	0/20	0/20	0/20	14/20*	20/20*
Focal Discoloration	0/20	0/20	0/20	2/20	5/20	6/20*
Female						
Enlargement	0/20	0/20	0/20	---	---	8/20*
Focal Discoloration	0/20	0/20	0/20	---	---	3/20

* $p < 0.05$

Table 9: Incidence of Histopathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Male						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	4	14**	20**	20**
Necrosis	1	0	2	4	8*	12**
Individual Cell	0	0	0	0	2	12**
Total Affected	1	0	2	4	10**	18**
Vacuolation	0	0	6*	2	3	10**
Individual Cell	0	0	0	0	0	6**
Total Affected	0	0	6*	2	3	16**
Female						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	0	---	---	17**
Necrosis	0	0	0	---	---	6*
Individual Cell	0	0	0			1
Total Affected	0	0	0			6*
Vacuolation	0	0	0	---	---	2
Individual Cell	0	0	0			1
Total Affected	0	0	0			3

* $p < 0.05$, ** $p < 0.01$

Reviewed by: Robert F. Fricke, Ph.D.
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Elizabeth A. Doyle, Ph.D.
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT 009419

STUDY TYPE: 90-day oral - Mouse (82-1) TOX. CHEM. NO.: 323EE

MRID NO.: 420505-02

009119

TEST MATERIAL: Propiconazole

SYNONYMS: CGA-64250

STUDY NUMBER: F-00107

SPONSOR: Ciba-Geigy Corp., Agricultural Division
P.O. Box 18300, Greensboro, NC 27419

TESTING FACILITY: Ciba-Geigy Corp., Environmental Health Center
400 Farmington Avenue, Farmington, CN 06032

TITLE OF REPORT: 13-Week Toxicity Study with CGA 64250 in Male Mice

AUTHOR: Robert F. Potrepka and John C. Turnier

REPORT ISSUED: April 30, 1991

CONCLUSIONS: For 13 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively).

NOEL = 20 ppm (LDT)

LOEL = 500 ppm (MDT1)

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

(Note: The study as submitted is flawed in that the interim and terminal sacrifice data were combined. The pathology incidence data for the 4, 8 and 13 week time points were obtained (via FAX) from the sponsor at the request of the primary reviewer and are appended to this report.)

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

5. Quality assurance was documented by signed and dated GLP and quality assurance statements.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of toxicity, moribundity and mortality.

a. Toxicity: There were no clinical observations attributable to the administration of the test article.

b. Mortality (survival): There were no unscheduled deaths during the study.

2. Body weight: Animals were weighed weekly during the 13 week treatment period.

a. Body Weight Data: Significant differences between the control and treated mean body weights were limited to animals in the 2500 ppm group during the first 8 weeks of the study (Table 1). A significant difference was also observed in the 1450 ppm group after 4 weeks.

b. Cumulative Body Weight Gain: The cumulative body weight gains showed significant decreases for animals in the 2500 ppm group during weeks 1, 2, and 4 (Table 1).

Table 1: Mean Animal Body Weights (g) and Cumulative Body Weight Gains

Week of Study	Body Weight (g)		Weight Gain (g)	
	0 ppm	2500 ppm	0 ppm	2500 ppm
1	29.7	27.6**	2.2	0.8**
2	31.2	29.5**	3.7	2.6**
3	32.4	31.0*	4.9	4.1
4	33.6	31.2**	6.1	4.3**
5	34.1	32.5**	6.6	5.7
6	34.7	33.0**	7.2	6.2
7	35.7	33.8**	8.2	7.0
8	35.7	33.8*	8.2	7.3

* $p < 0.05$, ** $p < 0.01$

c. Compound intake results: The average daily compound consumption is summarized below in Table 4.

Table 4: Average daily consumption of compound (mg/kg/day) at each dose level.

Dose Level (ppm)	Compound Consumption
20	2.7
500	65
850	112
1450	194
2500	352

4. Ophthalmological examinations: Examinations were performed on all animals at the termination of the study. No treatment-related eye lesions were observed.

5. Hematology and Clinical Chemistry: Clinical chemistry analyses were performed after 4 and 8 weeks of exposure and at the termination of the study (13 weeks). The checked (X) parameters were examined.

a. Hematology: Not performed

b. Clinical Chemistry

Electrolytes
- Calcium
- Chloride
- Magnesium
- Phosphorous
- Potassium
- Sodium

Enzymes
- X Alkaline phosphatase
- Cholinesterase
- Creatinine phosphokinase
- Lactic acid dehydrogenase
- X Serum alanine aminotransferase (SGPT, ALT)
- X Serum aspartate aminotransferase (SGOT, AST)
- X Sorbitol Dehydrogenase

Other
- Albumin
- Blood creatinine
- Blood urea nitrogen
- X Cholesterol
- Globulins
- Glucose
- Total Bilirubin
- Triglycerides
- Total Protein

Results: Significant clinical chemistry findings are shown in Table 5, below.

Table 6: Absolute and relative liver weights

Dose Level (ppm)	Absolute (g)	% of Body Weight	% of Brain Weight
0	1.307	4.524	266.7
00	1.194	4.335	251.1
500	1.523*	5.339**	317.8
850	1.709**	6.078**	356.5**
1450	1.984**	7.043**	414.5**
2500	2.382**	8.776**	512.0**

* $p < 0.05$, ** $p < 0.01$

b. Gross pathology: The only observations of toxicological significance were generalized enlargement and focal discoloration of the livers. The incidence data is presented in Table 7, below (See appended supplementary data).

Table 7: Incidence Data for Gross Pathological Observations in the Liver

Observation	Week of Study	Animals per Group	Dose Level (ppm)			
			0	850	1450	2500
Enlargement	4	10	0	1	3	10**
	8	10	0	6*	10**	10**
	13	20	0	7*	19**	20**
Prominent Lobular Architech.	4	10	0	0	0	1
	8	10	0	0	1	5
	13	20	0	0	5	12**

* $p < 0.05$, ** $p < 0.01$

c. Microscopic pathology

1) Non-neoplastic: Examination of the livers showed an increased incidence of histopathological findings are summarized in Table 8, below (See appended supplementary data). A dose-related increase in both the incidence and severity of hypertrophy, necrosis and vacuolation. Hypertrophy was mild to moderate with the more severe lesions occurring in the 1450 and 2500 ppm dose groups. Necrosis and vacuolation graded from minimal to moderate, and again, the

D. DISCUSSION: The objective of this study was to determine the MTD for the subchronic (13 week) administration of the test article to male mice. The test article was incorporated in the diet at 0, 20, 500, 850, 1450 or 2500 ppm. Significant increases in the absolute and relative liver weights at 500 ppm or higher correlated with gross pathological changes, histopathological changes and altered clinical chemistry findings. Hepatocellular hypertrophy, necrosis and vacuolation were significantly increased at 850 ppm, 1450 ppm and 2500 ppm, respectively. In general, the severity of the histopathological lesions was dose-related with the highest incidence of mild to moderate lesions occurring in the highest dose groups. None of the lesions, however, were characterized as either marked or severe. Serum cholesterol was decreased at 850 ppm or higher and serum alanine aminotransferase was increased at 1450 ppm or higher.

CONCLUSIONS: For 13 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively).

NOEL = 20 ppm (LDT)

LOEL = 500 ppm (MDT1)

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

(Note: The study as submitted is flawed in that the interim and terminal pathology data were combined. The pathology incidence data for the 4, 8 and 13 week time points were obtained (via FAX) from the sponsor at the request of the primary reviewer and are appended to this report.)

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

FISHER'S EXACT PROBABILITY
with Bonferroni correction

CRITERION	DOSE GROUP		INCIDENCE	PROBABILITY
F-00107 4-wk Enlarged	Control	m	0/ 10	-
	500 ppm		0/ 10	1.0000000
	850 ppm		1/ 10	0.9375000
	1450 ppm		3/ 10	0.3591131
	2500 ppm		10/ 10	0.0000216
F-00107 4-wk Focus	Control	m	0/ 10	-
	500 ppm		0/ 10	1.0000000
	850 ppm		2/ 10	0.6607986
	1450 ppm		3/ 10	0.3591131
	2500 ppm		5/ 10	0.0634476
F-00107 8-wk Discoloration	Control	m	0/ 10	-
	500 ppm		0/ 10	1.0000000
	850 ppm		0/ 10	1.0000000
	1450 ppm		2/ 10	0.6607986
	2500 ppm		5/ 10	0.0634476
F-00107 8-wk Enlarged	Control	m	0/ 10	-
	500 ppm		0/ 10	1.0000000
	850 ppm		6/ 10	0.0214965
	1450 ppm		10/ 10	0.0000216
	2500 ppm		10/ 10	0.0000216
F-00107 8-wk Prominent Lob Arc	Control	m	0/ 10	-
	500 ppm		0/ 10	1.0000000
	850 ppm		0/ 10	1.0000000
	1450 ppm		1/ 10	0.9375000
	2500 ppm		5/ 10	0.0634476
F-00107 13-wk Enlarged	Control	m	0/ 20	-
	500 ppm		0/ 20	1.0000000
	850 ppm		7/ 20	0.0165286
	1450 ppm		19/ 20	0.0000000
	2500 ppm		20/ 20	0.0000000
F-00107 13-wk Prom Lob Arch	Control	m	0/ 20	-
	500 ppm		0/ 20	1.0000000
	850 ppm		0/ 20	1.0000000
	1450 ppm		5/ 20	0.0009690
	2500 ppm		12/ 20	0.0000900

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Propiconazole, Male Mouse Dietary Study - Comparisons Among Pathologists - J.M. Offer, J. Hardisty and L.H. Brennecke of Hepatocellular Tumor Rates

Caswell no.323EE

From: Bernice Fisher, Biostatistician Bernice Fisher 3/30/
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

To: Elizabeth Doyle, Ph.D., Section Head
Review Section IV
Herbicide/Fungicide/Antimicrobial Support Branch
Health Effects Division (H7509C)

Thru: Kerry L. Dearfield, Ph.D., Acting Section Head
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

Dr. Doyle requested a comparison of 3 pathologist's (J.M. Offer, J. Hardisty and L.H. Brennnecke) observation of the number of hepatocellular tumors that occurred in the 2-year dietary study of propiconazole (CGA 64 250) in male mice.

Since only 0, 500 and 2500 ppm dose level tumors were re-evaluated by L.H. Brennecke, the statistical analysis of the comparative data from the 3 pathologists was based only on these dose levels (original study had an additional dose of 100 ppm).

Table 1. Propiconazole - Mouse Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53[a]	53-78	79-104[b]	Total
0	0/64	2/64	11/62	11/51	16/40	29/53(55)**
500	1/64	5/63	11/58	10/47	16/37	32/53(60)*
2500	5/64	5/59	9/54	16/45	15/29	41/55(75)*

+ Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 53.

[b] Final sacrifice at weeks 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

Table 3. Propiconazole - Male Mouse Study, Hepatocellular Carcinoma Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Carcinomas			
Pathologist			
J.M. Offer	15/62	15/60	26[a]/55
(%)	(24)	(25)	(47)
p=	0.003**	0.511	0.010*
J. Hardisty	16/62	13/60	25[b]/55
(%)	(26)	(22)	(45)
p=	0.006**	0.75(n)	0.035*
L.J. Brennecke	14/60	11/58	20[c]/54
(%)	(23)	(19)	(37)
p=	0.028*	0.801(n)	0.050

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first carcinoma.

n Negative change from control.

[a] First carcinoma observed at week 50, dose 2500 ppm.
[b] First carcinoma observed at week 50, dose 2500 ppm.
[c] First carcinoma observed at week 53, dose 2500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

References

Armitage, P. (1955) Tests for Linear Trends in Proportions, Biometrics 11, 375-386.

Cochran, W.G. (1954) Some Methods for Strengthening the Comon X^2 Test, Biometrics 10, 417-451.

Cox, D.R. (1972) Regression Models and Life Tables (with discussion) J. Royal Stat. Soc. Ser. B. 34, 187-220.

Thomas, D.G., Breslow, N., and Gart, J.J. (1977) Trend and Homogeneity Analysis of Proportions and Life Life Table Data, Computers and Biomedical Research 10, 373-381.

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Interim Sacrifice

In this review, treatment-related changes after 53 weeks consisted of increased incidences of hepatocellular adenomas in the 2500 ppm dose group (four adenomas in three high dose mice compared to one adenoma in controls); hepatocellular carcinomas in the 2500 ppm dose group (three carcinomas in three high dose mice compared to none in controls); and hepatocellular enlargement in the 500 ppm and 2500 ppm dose groups. The three mice with carcinomas each had adenomas as well.

A comparison of the data resulting from the first review by Dr. Hardisty, (R1), and this reviewer (R2) is presented in Table I-1. Applicable data from the original pathologist's evaluation were not available to this reviewer.

TABLE I-1
HEPATOCELLULAR NEOPLASMS IN INTERIM SACRIFICE MALE MICE

NEOPLASM	Groups (No. of Animals Examined)					
	CONTROL (11)		500 PPM (11)		2500 PPM (9)	
	R1[1]	R2	R1[1]	R2	R1[1]	R2
Adenoma	1/1*	1/1*	4/4*	2/2*	4/3*	4/3*
Carcinoma	0/0*	0/0*	0/0*	0/0*	3/3*	3/3*
No. of Mice with Adenomas only	1	1	4	2	1	1

* = Number of Neoplasms/Number of Animals with Neoplasms
[1] = Data obtained from Hardisty/EPL Report dated May 6, 1991. p. 5.

Terminal Sacrifice (Including Found Dead and Moribund Sac.)

In this review, treatment-related neoplastic changes consisted of a large increase in the incidence of hepatocellular adenomas (number of adenomas/number of animals with adenomas) in the 2500 ppm dose group (77/39) compared to controls (25/20) and a small increase in the incidence of hepatocellular carcinomas (number of carcinomas/number of animals with carcinomas) in the 2500 ppm dose group (23/17) compared to controls (15/14). There were no increases in the number of hepatocellular adenomas or carcinomas or animals having liver tumors in 500 ppm dose group.

In the 2500 ppm dose group, all but one of the hepatocellular carcinomas were in mice which died or were moribund sacrificed prior to terminal sacrifice. In nearly all cases, the carcinomas were very large tumors which caused the early death or moribund condition. Such was not the case in the 0 ppm and 500 ppm dose groups, in which the numbers of mice having carcinoma(s) in the early deaths were nearly the same as those in the terminal sacrifice. The numbers of mice having only hepatocellular adenoma(s) in the early death and terminal

The incidence of hepatocyte vacuolization in the 2500 ppm dose group was markedly increased compared to controls (30/55 vs. 5/53). There was no increase in the incidence of hepatocyte vacuolization in the 500 ppm dose group compared to controls.

The incidence of chronic inflammation in the 2500 ppm dose group was moderately increased compared to controls (41/55 vs. 28/53). There was no increase in the incidence of chronic inflammation in the 500 ppm dose group compared to controls.

The incidence of pigmented Kupffer cells in the 2500 ppm dose group was markedly increased compared to controls (33/55 vs. 3/53). There was no increase in the incidence of chronic inflammation in the 500 ppm dose group compared to controls.

SUMMARY AND CONCLUSION

The livers of male mice from the 0 ppm, 500 ppm and 2500 ppm dose groups were reviewed microscopically. There was a marked increase in the incidence of hepatocellular adenomas and a modest increase in the incidence of hepatocellular carcinomas in the 2500 ppm dose group but not in the 500 ppm dose group compared to controls. There was also a great increase in the incidence of foci of cellular alteration in the 2500 ppm dose group but a much smaller increase in the 500 ppm dose group compared to controls. Potential histologic indication of hepatotoxicity, as evidenced by increased incidences of hepatocyte enlargement, hepatocyte vacuolization, pigmented Kupffer cells, and chronic inflammation was present in the 2500 ppm dose group. A much smaller increase in the incidence of hepatocyte enlargement was present in the 500 ppm dose group compared to controls. No other evidence of hepatotoxicity was present in the 500 ppm dose group.

Lucas H. Brennecke, D.V.M.
Diplomate, ACVP
January 30, 1992

TABLE II-B
INCIDENCE OF LIVER LESIONS IN MALE MICE
CGA 64 250 (Propiconazole)
Early Deaths (Moribund Sacrifice/Found Dead)

Liver (No. of Animals Examined)	CONTROL (29)	500 PPM (32)	2500 ppm (41)
Hepatocellular Adenoma*	12/9	8/7	44/25
Hepatocellular Carcinoma*	9/8	9/6	22/16
Well Differentiated*	3/3	6/5	15/11
Moderately Well Differentiated*	6/6	3/2	6/4
Poorly Differentiated*	-	-	1/1
No. Animals with only Hep. Adenoma	6	3	14
Basophilic Focus	1	3	6
Eosinophilic Focus	1	2	9
Clear Cell Focus	1	0	0
Mixed Cell Focus	0	0	1
Hepatocyte Enlargement	7	16	35
Minimal	2	5	5
Mild	3	8	11
Moderate	2	3	19
Hepatocyte vacuolization	2	2	20
Minimal	-	-	9
Mild	1	2	7
Moderate	1	-	4
Hepatocyte Necrosis	3	0	6
Minimal	2	-	4
Mild	1	-	2
Inflammation, chronic	8	11	27
Minimal	5	8	15
Mild	3	3	10
Moderate	-	-	2
Pigmented Kupffer Cells	1	0	20
Minimal	1	-	6
Mild	-	-	12
Moderate	-	-	2
Histiocytic Sarcoma	1	0	0
Malignant Lymphoma	5	3	0
Myeloid Leukemia	1	0	0

Key: * = Numbers indicate Total Count/ No. of Animals

TABLE II-C
INCIDENCE OF LIVER LESIONS IN MALE MICE
CGA 64 250 (Propiconazole)
Terminal Sacrifice

Liver (No. of Animals Examined)	CONTROL (24)	500 PPM (21)	2500 ppm (14)
Hepatocellular Adenoma*	13/11	13/8	33/14
Hepatocellular Carcinoma*	6/6	6/5	1/1
Well Differentiated*	3/3	3/3	1/1
Moderately Well Differentiated*	2/2	2/2	-
Poorly Differentiated*	1/1	1/1	-
No. Animals with only Hep. Adenoma	6	7	13
Basophilic Focus	5	5	2
Eosinophilic Focus	0	2	8
Clear Cell Focus	0	0	1
Mixed Cell Focus	0	2	0
Hepatocyte Enlargement	13	14	14
Minimal	7	6	2
Mild	5	5	-
Moderate	1	3	9
Moderately Severe	-	-	3
Hepatocyte vacuolization	3	3	10
Minimal	3	-	1
Mild	-	2	9
Moderate	-	1	-
Hepatocyte Necrosis	2	0	0
Minimal	2	-	-
Inflammation, chronic	20	18	14
Minimal	10	13	7
Mild	7	3	6
Moderate	3	2	1
Pigmented Kupffer Cells	2	2	13
Minimal	2	2	5
Mild	-	-	8
Hemangioma	0	1	1
Malignant Lymphoma	0	1	0
Myeloid Leukemia	1	0	0
Cyst	0	1	0
Infarction	1	0	2

Key: * = Numbers indicate Total Count/ No. of Animals

TABLE II-D (continued)
INCIDENCE OF LIVER LESIONS IN MALE MICE
CGA 64 250 (Propiconazole)
Terminal Sacrifice and Early Deaths

Liver (No. of Animals Examined)	CONTROL (29)	500 PPM (32)	2500 ppm (41)
Amyloid	0	2	0
Angiectasis	0	0	2
Congestion	0	1	0
Cyst	0	1	0
Hematopoietic Cell Proliferation	2	1	0
Infarction	1	2	3
Leukocytosis	1	0	0

Key: * = Numbers indicate Total Count/ No. of Animals

PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: CONTROL SEX: MALE
FATES: INTERIM SACRIFICE

ANIMAL ID:	53	54	55	56	57	58	59	60	61	62
LIVER						N	N	N	N	
HEPATOCELLULAR ADENOMA*	-	1	-	-	-	-	-	-	-	-
HEPATOCYTE ENLARGEMENT	-	-	-	2	3	-	-	-	-	-
HEPATOCYTE VACUOLIZATION	-	1	1	-	2	-	-	-	-	1
INFLAMMATION, CHRONIC	1	1	1	-	-	-	-	-	-	-

30-Jan-1992

009419

PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 500PPM SEX: MALE
FATES: INTERIM SACRIFICE

ANIMAL ID:	181	182	183	184	185	186	187	188	189	191
LIVER										
HEPATOCELLULAR ADENOMA*	1	-	-	-	-	-	-	-	1	-
BASOPHILIC FOCUS	-	-	-	-	-	-	-	-	-	3
HEPATOCYTE ENLARGEMENT	2	1	2	1	-	1	1	1	2	1
HEPATOCYTE VACUOLIZATION	-	-	-	-	2	2	-	1	1	-
INFLAMMATION, CHRONIC	-	-	-	-	-	1	-	-	-	-

30-Jan-1992

PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 2500PPM SEX: MALE
FATES: INTERIM SACRIFICE

ANIMAL ID:	245	247	249	250	251	252	253	254	255
LIVER									
HEPATOCELLULAR ADENOMA*	1	.	2	1	.	.	.	.	.
NC, WELL DIFFERENTIATED*	.	.	1	1	1	.	.	.	.
HEPATOCYTE ENLARGEMENT	1	3	3	3	3	3	3	2	3
HEPATOCYTE NECROSIS	2	1	.	.	.	.	.	.	.
INFLAMMATION, CHRONIC	1	1	.	.	1	1	1	.	1
PIGMENTED KUPFFER CELLS	1	.	.	.	.	.	.	.	.

(End of Report) 30-Jan-1992

PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: CONTROL SEX: MALE
FATES: EARLY DEATH

ANIMAL ID:	20	22	24	26	30	32	33	34	36	37
LIVER		N		A						
HEPATOCELLULAR ADENOMA*	-	-	1	-	-	-	1	-	-	-
HC, WELL DIFFERENTIATED*	-	-	1	-	-	-	-	-	-	-
HC, MOD WELL DIFFERENTIATED*	-	-	1	-	1	1	-	-	-	-
BASOPHILIC FOCUS	-	-	-	-	-	3	-	-	-	-
EOSINOPHILIC FOCUS	-	-	2	-	-	-	-	-	-	-
HEPATOCYTE ENLARGEMENT	1	-	3	-	-	-	-	-	-	-
INFLAMMATION, CHRONIC	-	-	2	-	-	-	-	-	-	-
MALIGNANT LYMPHOMA	-	-	-	-	-	-	-	P	P	P
MYELOID LEUKEMIA	-	-	-	-	-	P	-	-	-	-

30-Jan-1992

PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 500PPM SEX: MALE
FATES: EARLY DEATH

ANIMAL ID:	132	134	135	139	141	142	143	144	145	146
LIVER									N	
HEPATOCELLULAR ADENOMA*	1	-	-	-	-	-	-	-	-	-
HC, WELL DIFFERENTIATED*	1	-	-	-	-	-	-	-	-	-
BASOPHILIC FOCUS	-	-	-	3	-	-	-	-	-	-
HEPATOCYTE ENLARGEMENT	2	-	-	1	2	1	3	2	-	3
HEPATOCYTE VACUOLIZATION	-	-	-	-	-	2	-	-	-	-
INFLAMMATION, CHRONIC	1	-	-	-	-	1	-	-	-	-
MALIGNANT LYMPHOMA	-	P	-	-	-	-	P	-	-	-
AMYLOID	-	-	-	-	-	-	-	3	-	-
INFARCTION	-	-	4	-	-	-	-	-	-	-

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Tabulated Animal Data

GROUP: 500PPM SEX: MALE
FATES: EARLY DEATH

ANIMAL ID:	166	168	169	170	171	172	173	176	178	179
LIVER										
HEPATOCELLULAR ADENOMA*		N	N	N		N				
HC, MOD WELL DIFFERENTIATED*	1	-	-	-	-	-	-	-	-	1
BASOPHILIC FOCUS	-	-	-	-	-	-	-	-	1	-
EOSINOPHILIC FOCUS	-	-	-	-	-	-	-	-	-	2
HEPATOCYTE ENLARGEMENT	-	-	-	-	-	-	-	2	-	-
INFLAMMATION, CHRONIC	3	-	-	-	1	-	1	2	-	1
AMYLOID	-	-	-	-	1	-	2	1	-	-
CONGESTION	-	-	-	-	-	-	-	-	2	-
INFARCTION	3	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	4	-	-

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PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 2500PPM SEX: MALE
FATES: EARLY DEATH

ANIMAL ID:	193	194	195	196	197	199	202	203	206	207
LIVER	M									
HEPATOCELLULAR ADENOMA*	-	1	1	3	-	-	2	-	4	1
HC, WELL DIFFERENTIATED*	-	-	-	-	1	2	1	-	-	-
HC, MOD WELL DIFFERENTIATED*	-	-	-	-	-	-	-	2	-	1
BASOPHILIC FOCUS	-	-	-	-	3	-	-	-	-	-
HEPATOCYTE ENLARGEMENT	-	3	3	3	-	3	-	2	3	3
HEPATOCYTE VACUOLIZATION	-	2	2	3	-	-	-	-	1	2
HEPATOCYTE NECROSIS	-	1	-	-	-	-	-	-	-	-
INFLAMMATION, CHRONIC	-	1	1	1	1	-	-	1	1	2
PIGMENTED KUPFFER CELLS	-	-	2	-	3	-	-	1	2	2

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FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 2500PPM SEX: MALE
FATES: EARLY DEATH

ANIMAL ID:	221	222	224	225	226	227	228	230	231	232
LIVER										
HEPATOCELLULAR ADENOMA*	1	1	2	1	1	2	1	-	-	2
HC, WELL DIFFERENTIATED*	-	-	2	-	1	-	1	1	-	-
HC, MOD WELL DIFFERENTIATED*	-	-	-	-	-	-	-	-	-	1
BASOPHILIC FOCUS	-	-	1	-	-	-	-	-	-	3
EOSINOPHILIC FOCUS	2	-	3	-	2	-	-	-	-	-
HEPATOCYTE ENLARGEMENT	3	3	2	3	2	2	3	3	2	3
HEPATOCYTE VACUOLIZATION	-	-	1	-	-	-	1	-	-	1
HEPATOCYTE NECROSIS	2	1	-	-	-	1	-	-	-	-
INFLAMMATION, CHRONIC	2	1	-	1	1	2	2	2	-	2
PIGMENTED KUPFFER CELLS	2	-	-	1	1	2	-	2	-	2
ANGIECTASIS	-	-	-	-	2	-	-	-	-	-

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HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 2500PPM SEX: MALE
FATES: EARLY DEATH

ANIMAL ID:	256
LIVER	N

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PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: CONTROL SEX: MALE
FATES: TERMINAL SACRIFICE

ANIMAL ID:	23	25	27	28	29	31	35	39	40	41
LIVER				M						
HEPATOCELLULAR ADENOMA*	2	-	-	-	1	1	1	-	1	1
HC, WELL DIFFERENTIATED*	-	-	-	-	-	-	1	-	-	-
HC, MOD WELL DIFFERENTIATED*	-	-	-	-	-	1	-	-	-	-
BASOPHILIC FOCUS	1	-	-	-	-	-	-	-	-	-
HEPATOCYTE ENLARGEMENT	-	-	-	-	1	-	3	2	2	1
HEPATOCYTE VACUOLIZATION	1	-	-	-	1	-	-	1	-	-
HEPATOCYTE NECROSIS	-	1	-	-	-	-	-	-	-	-
INFLAMMATION, CHRONIC	1	2	2	-	2	3	1	1	3	1
INFARCTION	-	-	-	-	-	-	-	-	4	-

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PATHOLOGY ASSOCIATES, INC.
HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 500PPM SEX: MALE
FATES: TERMINAL SACRIFICE

ANIMAL ID:	129	130	131	133	136	137	138	140	150	151
LIVER										
HEPATOCELLULAR ADENOMA*	.	1	2	.	.	.	.	.	2	.
HC, WELL DIFFERENTIATED*	.	.	1	.	.	.	.	.	.	.
HC, MOD WELL DIFFERENTIATED*	.	.	.	1	.	.	.	.	.	.
BASOPHILIC FOCUS	.	.	2	.	.	2	.	.	3	.
EOSINOPHILIC FOCUS	.	.	.	.	.	.	3	.	.	.
MIXED CELL FOCUS	.	.	.	.	.	.	.	.	.	4
HEPATOCYTE ENLARGEMENT	.	.	1	1	.	1	1	.	3	2
HEPATOCYTE VACUOLIZATION	.	.	.	.	3	.	2	.	.	2
INFLAMMATION, CHRONIC	1	3	2	.	2	1	1	.	1	2
PIGMENTED KUPFFER CELLS	1	1	.	.	.	.	.	.	.	.
HEMANGIOMA	.	.	.	P	.	.	.	.	.	.
MALIGNANT LYMPHOMA	.	.	.	.	.	.	.	P	.	.

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HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 500PPM SEX: MALE
FATES: TERMINAL SACRIFICE

ANIMAL ID:	177
LIVER	
HEPATOCELLULAR ADENOMA*	3
HEPATOCYTE ENLARGEMENT	1
INFLAMMATION, CHRONIC	1

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HISTOPATHOLOGIC REVIEW OF LIVER IN MALE MICE
FROM THE LONG-TERM FEEDING STUDY IN MICE
WITH CGA 64 250 (PROPICONAZOLE)

Tabulated Animal Data

GROUP: 2500PPM SEX: MALE
FATES: TERMINAL SACRIFICE

ANIMAL ID:	236	237	240	242
LIVER				
HEPATOCELLULAR ADENOMA*	1	4	1	1
BASOPHILIC FOCUS	-	2	-	-
EOSINOPHILIC FOCUS	3	-	2	3
HEPATOCYTE ENLARGEMENT	4	3	3	1
HEPATOCYTE VACUOLIZATION	2	-	2	-
INFLAMMATION, CHRONIC	1	2	3	1
PIGMENTED KUPFFER CELLS	1	2	2	1
INFARCTION	-	4	-	-

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END